REMARKS

Claims 1-7 and 14-29 are presently pending. Amendments to the claims are discussed below. No new matter has been added herewith. The following addresses the substance of the Final Office Action.

Obviousness

Kraus et al. in view of Piet et al. and Anderle et al.

Claims 1-6, 14, 16-19, 21-24 and 26-29 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Kraus et al. (U.S. Patent No. 5,143,838) in view of Piet et al. (1990 *Transfusion* **30**:591-598) and Anderle et al. (U.S. Patent Application publication No. 2003/0133829). Kraus et al. discloses conversion of prothrombin to thrombin on an anion exchange column but does not teach solvent-detergent inactivation on the anion exchange medium or sterilization of plasma prior to fractionation. Piet et al. teaches that virus sterilization methods can be applied at the time of plasma collection, prior to fractionation procedures. The process disclosed in Anderle et al. involves the use of a detergent in specific combination with a carboxylic acid ester solvent. Anderle et al. indicates that, with this specific combination of a carboxylic acid ester and detergent, pathogens in a protein solution are effectively inactivated while the protein activity is substantially fully preserved (see paragraph [0014] of Anderle).

The presently claimed methods are different from the method disclosed by Kraus et al. in that the inactivation of virus occurs before and/or after Factor X, or Factor X and prothrombin, are loaded onto an anion exchange medium and continues until the anion exchange medium is washed to remove the solvent and detergent. The Examiner acknowledged at page 6 of the Office Action that Kraus et al. do not teach solvent-detergent inactivation on the anion exchange medium. The present methods allow inactivation of virus, essentially without introducing an extra step, other than washing off the solvent and detergent prior to activation of prothrombin to form thrombin. Thus, the present methods allow removal of the solvent-detergent reagents from the anion-exchanger and the subsequent generation of activated Factor X and then thrombin in a single chromatographic step. The methods of the invention therefore avoid the need for a separate step to remove the S/D reagents prior to loading the Factor X and prothrombin onto the column, and/or a separate step to remove the reagents from the thrombin once generated.

Anderle et al. Teaches Away From Using TNBP

In contrast to Anderle et al., the S/D inactivation step in the presently claimed methods specifically utilizes TNBP as solvent, and not a carboxylic acid ester, as was specifically required by the methods of Anderle et al. Indeed, Anderle et al. teaches away from using TNBP in a S/D treatment prior to activation of prothrombin to yield thrombin. In particular, Anderle et al. cautioned at paragraph [0005] that there is a serine protease group, which includes the prothrombin complex of coagulation factors, which are sensitive to, and at least partially deactivated by conventional S/D methods. For these proteins, Anderle et al. recommends that detergent alone may be used at high concentrations (i.e., without solvent such as TNBP, in particular).

Moreover, during the telephonic interview, the Examiner noted that Anderle et al. concluded at paragraph [0086] that "A composition comprising a carboxylic acid ester, in particular acetyl triethyl citrate and tributyl or triethyl citrate has a strong inactivating effect on pathogens and is however sufficiently gentle and safe in order to preserve a high level of protein function and activity to the contrary of the known combinations as for example Tween 80 with TNBP which reduces the activity of the protein." Thus, one of ordinary skill in the art would be discouraged from using the presently claimed S/D treatment, which specifically uses TNBP as solvent. In light of the teaching away by Anderle et al., it would not be obvious to the skilled artisan to treat prothrombin with a conventional S/D treatment, let alone load prothrombin/solvent/detergent onto an anion exchange medium.

The Presently Claimed Methods Go Against Conventional Understanding

The Examiner concluded that Piet et al. provides motivation to use TNBP and detergent to sterilize plasma in the method of Kraus et al. prior to obtaining fractions because Piet et al. al teach that sterilization methods can be applied at the time of plasma collection, prior to fractionation procedures. However, the skilled artisan would have also been aware of the clear and specific teachings of Anderle et al., which would have led the skilled artisan to avoid the use of TNBP with prothrombin. If anything, the skilled artisan would have developed a method that employed a carboxylic acid ester as solvent (e.g., acetyl triethyl citrate and tributyl or triethyl citrate) instead of TNBP.

Referring to Item 7 of the Rule 132 Declaration by Dr. Peter Feldman, Dr. Feldman states:

> "In view of the teachings of Anderle et al., a skilled person would have been discouraged from inactivating a solution containing prothrombin and/or Factor X with TNBP and detergent. Instead, the teachings of Anderle et al. would have directed a skilled artisan to use a combination of a carboxylic acid ester and detergent."

Based on the combined teachings of Kraus et al. Piet et al. and Anderle et al., the skilled artisan would have had been discouraged from developing the presently claimed methods, wherein thrombin is activated after a specific TNBP-detergent virus inactivation step. The skilled artisan would not combine the teachings of Kraus et al. Piet et al. and Anderle et al. to arrive at the presently claimed methods because Anderle et al. specifically cautions against using any solvent other than a carboxylic ester in combination with detergent to activate pathogens in a prothrombin-containing solution.

Despite the known problems with using TNBP as solvent, the Applicant unexpectedly discovered that these problems could be avoided by first treating a prothrombin-containing fraction with TNBP and a detergent in the presence of Factor X. After this treatment, the entire fraction containing prothrombin, Factor X, TNBP and detergent is then loaded onto an anion exchange medium, followed by washing the anion exchange medium to remove TNBP and detergent. At that point, the Factor X can be activated by metal ions while still on the anion exchange medium to yield Factor Xa, which converts prothromin to thrombin. In view of Anderle's teachings that the S/D technique using TNBP as a solvent will deactivate prothrombin, the foregoing technique went against conventional wisdom and unexpectedly produced thrombin in high yields and at high specific activity.

The Presently Claimed Methods Provide a Critical Limitation over the Prior Art

The presently claimed methods utilize a TNBP/detergent treatment step prior to activation of Factor X wherein the TNBP and detergent are removed by a washing step prior to subsequent activation of Factor X to yield Factor Xa, which converts prothrombin to thrombin. Referring to Items 8-15 of Dr. Feldman's declaration, the Applicant has discovered that it is important that the activation to form thrombin occurs on the anion exchange medium, and that the solvent and detergent reagents are removed from the anion exchange medium prior to activation of Factor X. None of the cited references disclose this critical distinction. Moreover, in view of the teaching

away by Anderle et al., the presently claimed methods go against the conventional understanding with regard to producing thrombin from prothrombin. Accordingly, Applicant respectfully asserts that the presently claimed methods are not obvious in view of the prior art of record.

In view of the foregoing remarks, the Applicant respectfully requests that the rejection under 35 U.S.C. § 103(a) with regard to Claims 1-6, 14, 16-19, 21-24 and 26-29 be withdrawn.

Kraus et al. in view of Piet et al., Anderle et al., Kingdom et al. and Heimburger et al.

Claims 7, 15, 20 and 25 remain rejected under 35 U.S.C. § 103(a) as being unpatentable over Kraus et al. (*supra*) in view of Piet et al. (*supra*), Anderle et al. (*supra*), Kingdom et al. (U.S. Patent No. 5,354,682) and Heimburger et al. (U.S. Patent No. 6,346,277). However, in view of remarks above in connection with Kraus et al., Piet et al. and Anderle et al., neither Kingdom et al. nor Heimburger et al. provide any additional information that show that the presently claimed methods are *prima facie* obvious. As such, the Applicant respectfully requests that the rejection of Claims 7, 15, 20 and 25 be withdrawn.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Co-Pending Applications of Assignee

Applicant wishes to draw the Examiner's attention to the following co-pending applications of the present application's assignee.

Docket No.	Serial No.	Title	Filed
FDEHN7.002APC	10/520436	PROCESSES FOR THE PREPARATION OF FIBRINOGEN	17-Aug-2006

CONCLUSION

In view of Applicants' amendments to the Claims and the foregoing Remarks, it is respectfully submitted that the present application is in condition for allowance. Should the Examiner have any remaining concerns which might prevent the prompt allowance of the application, the Examiner is respectfully invited to contact the undersigned at the telephone number appearing below.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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